

PATENT

APPLICATION FOR UNITED STATES LETTERS PATENT

for

METHOD FOR INDUCED LACTATION

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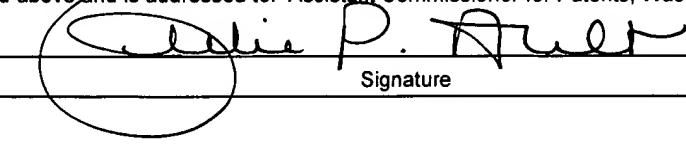
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This application claims priority to Provisional Application Serial No. 60/220,012 filed July 21, 2001.

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

5 The present invention relates to the field of enhancing milk production in mammals. More particularly, it concerns pharmaceutical compositions and methods of using said compositions in a manner effective to induce milk production in previously non-lactating animals.

2. TECHNICAL PROBLEM ADDRESSED BY THE INVENTION

10 Commercial raising of cattle for dairy production requires proper management. In addition to the various husbandry concerns such as herd health and nutrition, a critical management area for economic survival of any cattle operation, is the breeding management of the cows. In the case of dairy cows, the cows will not produce milk unless they have a calf, which is again dependent upon successful breeding management.

15 The timing of breeding and breeding intervals generally have great economic significance in dairy operations. Dairy cows are managed intensively and there are costs associated with breeding the cow, how long it takes each cow to become pregnant, as well as associated labor costs; economics of a dairy make it important to both minimize 20 the amount of time a dairy cow is not pregnant and yet still have a high probability of the cow becoming pregnant.

25 If a cow is successfully bred, she will become pregnant for approximately 280 days. Dairy cows are managed such that they are ideally bred and become pregnant again 45 to 60 days after calving.

It is estimated that for every day past a set goal date that a cow remains non-pregnant or open, there is an economic loss of between \$1.00-\$3.00 per day. For an average sized dairy herd that is between 200 to 1,000 cows, if the 24 hours during which the cow should be bred is missed for each cow, this represents an economic loss of 5 \$4,200.00 to \$21,000.00 annually. Often cows are not successfully bred for as many as 3 estrous cycles, due to infertility, infections and semen-related problems. If one half of the cows in a herd of 200 to 1,000 is not impregnated for 3 cycles, the estimated economic loss increases to \$6,300.00 to \$31,500.00 annually. These projections of economic loss to the producer demonstrate the critical importance of the cow spending the majority of each 10 year producing milk.

Annually 1 million dairy cows are culled for reproductive failure. It is estimated that dairies would retain approximately half of these cows if they were lactating.

15 To improve the management of dairy cows and decrease the economic losses associated with the non-pregnant interval it is desirable to have additional options and management tools other than culling animals. There is an estimated cost of approximately \$900.00 per animal culled for a dairy in addition to the costs incurred for days the animal is at the dairy prior to the decision to replace the animal. The option to 20 be able to selectively use hormonally-induced lactation as a management tool, is desirable. One example of where induced lactation might be an appropriate option is with problem breeder animals of excellent genetic background.

25 Scientists have been attempting to induce lactation artificially in dairy cows for over 30 years. In general, the studies have involved long hormone administration with low rates of success.

The instant invention provides a method for inducing lactation in a high proportion of mammals; wherein neither the ability to induce lactation, nor the milk yield is affected by the season.

5 DESCRIPTION OF RELATED ART

It is known that mammary cell proliferation and lactation are both stimulated by ovarian and pituitary hormones (for review see Erb, 1976). Since 1939, attempts have been made to induce lactation (Meites, 1961) using ovarian hormones (or their analogs), 10 but with limited success (milk yields averaging 60% of normal). Substantial progress was made in the 70's when reserpine (Collier et al, 1977) or dexamethasone (Fulkerson et al., 1975) were added to the regimen. Photoperiod (season) also impacts mammary development (Petitclerc, et al., 1985) and this may restrict the ability to artificially induce lactation in countries which utilize seasonal calving. Thus, variability among cows, 15 possible limitations due to day length, and management difficulties surrounding daily injections have resulted in there being only a limited interest in the area of induced lactation.

20 Davis et al., (1983) described an intra-vaginal sponge for the continuous delivery of ovarian steroids eliminating the need for daily injection. Using this device, the group reported an 89% success rate when an adjunct injection of dexamethasone was given with their regimen. More recently, Kensinger et al., (1998) included POSILAC® somatotropin in the induction protocol and obtained a 17% increase in milk yield compared to cows treated with steroids alone.

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Nevertheless, while the induction of lactation has the potential to increase farm profitability by allowing retention of reproductive culls, prior to the present invention, known methods have characteristically produced highly variable results, with respect to both the number of cows that produced milk and the amount of milk they produced (*see*

Head, 1999). While numerous factors, including day length, season of induction, length of dry period, and stage of estrous cycle, have been cited as potentially contributing to this variation (Kensinger, et al., 1979; Peel, et al., 1979; and Smith, et al., 1973), no means for limiting or eliminating the variation had been found prior to the development 5 of the present invention. Therefore, there remains a significant need, in the art, for methods of reproducibly inducing lactation in a high percentage of an animals, regardless of the season.

SUMMARY

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The present invention provides methods for effecting mammary secretion of milk in a mammal. The disclosed methods are particularly useful for inducing lactation without the benefit of a immediately preceding pregnancy. The mammal is preferably a bovine. Even more preferably, the mammal is a dairy heifer or a dairy reproductive cull.

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In one embodiment, the method comprises administering to an animal an estrogen-like agent (ELA) (e.g. estradiol) and a progestational agent (PGA) (e.g. progesterone) sufficient to maintain a milk-secretion stimulating amount of each agent for approximately 7 consecutive days, wherein the day of the first administration is defined 20 to be day 0; and administering a somatotropin, which is biologically active in the animal, in an amount sufficient to maintain a milk-secretion stimulating amount for 20 or more days from day 0.

In another embodiment the method comprises inducing lactation in a non-pregnant animal by administering to the animal a milk-secretion stimulating amount of an 25 ELA and a PGA for approximately 7 consecutive days, wherein the day of the first administration is defined to be day 0; also administering a milk-secretion stimulating amount of somatotropin for the animal to have bioavailability to the somatotropin for 20 or more days from day 0.

In any embodiment the method may optionally further comprise administering a milk-secretion enhancing amount of a glucocorticoid (e.g. dexamethasone) approximately 6 days after the last ELA administration.

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In any embodiment the method may optionally further comprise controlling the photoperiod length the animal is exposed to, either by the use of artificial lighting or selection of time of year when the method is employed, changing the melatonin levels in the animal, or any other effective means.

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In any embodiment the method may optionally further comprise physical stimulation of the mammal's mammary gland region for a selected time interval, preferably starting on the day following the last estradiol injection for 7 consecutive days.

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In any embodiment somatotropin can be further administered throughout the lactation of the animal.

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The instant invention is also directed to a method of using a combination of an ELA, a PGA, natural or synthetic somatotropin, and a glucocorticoid to induce lactation in a non-lactating mammal.

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The inventors, surprisingly, discovered that, using the methods described herein, dairy cattle can be induced to lactate and that the effectiveness of that induction is not dependent on the season. Furthermore, lactation can be induced without the benefit of an immediately preceding pregnancy. Consequently, the method is especially useful for inducing lactation in animals which have never been pregnant (such as dairy heifers) and animals which are no longer capable of pregnancy (such as dairy reproductive culls).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graph comparing the weekly average milk production for cows induced into winter-phase (FEB) and summer-phase (JUN) lactation as described in
5 Example 1.

Figure 2 is a graph showing the weekly average milk production for each individual cow induced into winter-phase lactation in Example 1.

10 Figure 3 is a graph showing the weekly average milk production for each individual cow induced into summer-phase lactation in Example 1.

15 Figure 4 is a graph showing plasma estradiol in animals implanted with pelleted estradiol benzoate or given an estradiol injection (2 mg on day 0).

15 Figure 5 is a graph showing plasma progesterone in animals implanted with pelleted progesterone (100 mg on day 0).

DESCRIPTION OF PREFERRED EMBODIMENTS

20 The present invention is a method for effecting mammary secretion of milk from an animal. As used herein “animal” is defined to include all mammals, including humans. The present invention is particularly useful for inducing lactation in an animal without the benefit of an immediately preceding pregnancy. Thus the present invention is
25 useful for inducing lactation in animals, such as dairy heifers, which have never been pregnant or in animals which are no longer capable of becoming pregnant (e.g. dairy reproductive culls).

As used herein the terms "administer", "administered", and "administration" of the various substances (e.g., progesterone, 17 β -estradiol, and etc.), denote providing an additional amount of the substance into the animal's bloodstream on the indicated days, whether via daily or other injections on those days or by release on those days from a 5 parenterally administered prolonged release delivery system (e.g., pellet, liquid depot, vaginal suppository or the like), or by continuous dosing (e.g., by an infusion pump) of the substance, delivered parenterally at the beginning of the time period, or, in the case of the continuous dose, throughout the time period. Alternatively it may refer to the delivery of the dosage by periodic (e.g. daily) parenteral injection or implantation or the 10 like.

As used herein, the terms "milk-secretion stimulating," "milk-secretion enhancing," "milk-secretion maintaining," and "milk-secretion sustaining" amounts of the various treatments to be administered to the animal (i.e. ELA, PGA, somatotropin, dexamethasone, and/or photo-period adjustment), are to be understood as being the 15 amounts of each individual substance or treatment which is required to cause and/or enhance milk-secretion in the presence of the other substances being co-administered. These terms are not meant to indicate the amounts of the individual substance or treatment that would be required to induce milk-secretion by themselves (e.g., treatment with dexamethasone alone).

20 In each embodiment of the instant invention, the somatotropin administered to the animal is one which is biologically active in said animal. It is proposed that the somatotropin may act, at least partially, by stimulating mammary cell growth and differentiation. This action may be direct, indirect (e.g. through intermediate factors such insulin-like growth factor-1, IGF-1), or both direct and indirect. The Inventor's disclose 25 this possible mode of action for somatotropin, without limiting the invention thereto.

One of ordinary skill in the art will appreciate that the somatotropin may be administered in any manner consistent with the instant invention. The somatotropin is

typically given in an amount of approximately 250 mg to 750 mg, with about 500 mg being preferable. The skilled artisan will appreciate that this amount of somatotropin can be delivered in a variety of ways and at a number of different dose levels (depending on the frequency of administration). In a preferred embodiment the somatotropin is 5 administered in a sustained-release formulation. More preferably the somatotropin is administered to the animal until at least day 20 of the treatment, even more preferably until at least day 30 (e.g. on days 0, 10, 20 and 30). Most preferably somatotropin is administered as a sustained release dose throughout lactation.

Those skilled in the art will also recognize that any natural or synthetic analog of 10 the somatotropin having approximately the equivalent bioactivity of the somatotropin native to the animal (e.g. bovine somatotropin used in cattle) may also be used. Approximately equivalent bioactivity as used herein would be at least 50% of the bioactivity of the somatotropin. Preferably such analog would have at least 75% of the 15 equivalent bioactivity, more preferably 90% of the equivalent bioactivity and most preferably 100% or greater than 100% of the bioactivity equivalent to the somatotropin.

Although 17 β -estradiol is used as the ELA in the exemplary embodiments herein, those skilled in the art will recognize that the ELA may be any natural or synthetic analog of 17 β -estradiol or any other substance having, when administered to the animal, a bioactivity approximately equivalent to the bioactivity of 17 β -estradiol. As used herein 20 the term "bioactivity" refers to the ability to produce a physiological response in the animal. An "approximately equivalent bioactivity" as used herein would be at least 50% of the equivalent bioactivity of 17 β -estradiol. Preferably such analog would have at least 75% of the equivalent bioactivity, more preferably 90% of the equivalent bioactivity and most preferably 100% or greater than 100% of the bioactivity equivalent to 17 β -estradiol. 25 The ELA may be given in any dose that is consistent with the present invention. Preferably, the ELA is provided in a dose of approximately 0.007 to 0.7 mg/kg body weight, more preferably about 0.07 to 0.7 mg/kg body weight, most preferably about 0.7 mg/kg body weight.

Similarly, although progesterone is used as the PGA in the exemplary embodiments herein, those skilled in the art will recognize that PGA may be any natural or synthetic analog of a progesterone or any other substance having, when administered to the animal, a bioactivity approximately equivalent to the bioactivity of the progesterone. An “approximately equivalent bioactivity” as used herein would be at least 5% of the equivalent bioactivity of progesterone. Preferably such analog would have at least 75% of the equivalent bioactivity, more preferably 90% of the equivalent bioactivity and most preferably 100% or greater than 100% of the bioactivity equivalent to progesterone. The PGA may be given in any dose that is consistent with the present invention. Preferably, the ELA is provided in a dose of approximately 0.0175 to 1.75 mg/kg body weight, more preferably about 0.175 to 1.75 mg/kg body weight, most preferably about 1.75 mg/kg body weight.

The ELA and PGA may be delivered by any means consistent with the instant invention. In one embodiment of the invention the ELA and PGA are administered parenterally as a pellet at the beginning of the treatment. In a preferred embodiment of this aspect of the invention the ELA are subcutaneously implanted as a slow release pellet. Even more preferably the ELA and PGA are respectively 17 β -estradiol and progesterone and are administered subcutaneously as slow-release pellets, wherein the 17 β -estradiol pellet comprises approximately 0.7 mg/kg body weight 17 β -estradiol, and wherein the progesterone pellet comprises approximately 1.75 mg/kg of body weight progesterone

In an alternative embodiment of the invention the ELA and PGA are injected subcutaneously twice daily (approximately every 12 hours) for 5-12 consecutive days, preferably 7 consecutive days. In a preferred aspect of this embodiment of the invention the ELA and PGA are respectively 17 β -estradiol and progesterone delivered at a dose of approximately 0.001 to 0.1 mg/kg body weight, preferably 0.01 to 0.1 mg/kg body weight 17 β -estradiol and 0.0025 to 0.25 mg/kg body weight 0.025 to 0.25 mg/kg body weight progesterone.

ELA and PGA administration should be sufficient to produce and maintain blood ELA and PGA levels, at concentrations sufficient to stimulate milk-secretion. Preferably, the ELA and PGA levels are maintained over a period of approximately 5 to 12 days, with 7 days being most preferable in cows.

5 Any embodiment may optionally further comprise the use of a single administration of a milk-secretion enhancing amount of a glucocorticoid. Preferably, the glucocorticoid is dexamethasone, nevertheless, the ordinarily skilled artisan will appreciate that other glucocorticoids may function in a similar fashion. Typically, dexamethasone is administered, to the animal, on about day 10 to about day 17 of the
10 treatment, preferably approximately 7 days after the discontinuation of the ELA and PGA. More preferably, the dexamethasone is administered on approximately day 13 of the treatment. It is believed that, when used, dexamethasone It is believed that the glucocorticoid treatment acts, at least partially by ensuring that the mammary gland cells
15 differentiate fully from the “growing state” to the “milk-secreting” state. During normal gestation, this differentiation takes place near parturition as the glucocorticoid levels rise and the glands begin to secrete milk. Thus, it is proposed that when the glucocorticoid (e.g. dexamethasone) is administered to the animal, in accordance with the methods of the instant invention, the increased glucocorticoid level in the animal enhances the function
20 of one or more of the cellular signaling cascades involved in orchestrating the physiological changes which must occur before milk production can begin. The Inventor's disclose this possible mode of action for the glucocorticoid, without limiting the invention thereto. The glucocorticoid is typically given at a dose of approximately 0.005 to 0.5 mg/kg body weight, preferably, approximately 0.05 to 0.5 mg/kg, and most preferably approximately 0.05 mg/kg.
25 Those skilled in the art will also recognize that any natural or synthetic glucocorticoid having approximately the equivalent bioactivity of dexamethasone may also be used. Approximately equivalent bioactivity as used herein would be at least 50% of the bioactivity of dexamethasone. Preferably such analog would have at least 75% of the

equivalent bioactivity, more preferably 90% of the equivalent bioactivity and most preferably 100% or greater than 100% of the bioactivity equivalent to dexamethasone.

Any embodiment may optionally further comprise controlling the amount of photoperiod to which the animal is exposed. Those skilled in the art will recognize that 5 some species of animal have seasonal fertility (e.g., animals such as sheep are only fertile during specific times of the year) which is influenced by length of photoperiod. Some animals are more fertile during decreasing photoperiods and some animals have increasing fertility in response to increasing photoperiod. The amount of photoperiod can be influenced by the use of housing with artificial lights, for example. A fixed 10 photoperiod may be used in the embodiments or a schedule of changing photoperiod, i.e., increasing or decreasing photoperiod may be employed, depending on the animal and the desired level of response.

Any embodiment may optionally include starting the treatment method at a specific time in a female animal's reproductive cycle. Those skilled in the art will know 15 that reproductive status and cycle can be easily determined, and if desired, synchronized by the use of an appropriate regimen of reproductive hormone administration. Such schedules and management are well known in the art.

Any embodiment may optionally include physical stimulation of the mammary gland. The mammary gland stimulation is preferably administered at least once daily 20 starting on about day 6 of the treatment (as counted from a treatment beginning on day 0) and continuing for at least 7 consecutive days. More preferably the physical stimulation is administered twice daily at approximately evenly spaced intervals and most preferably the mammary gland is stimulated three times a day at approximately evenly spaced intervals. The physical stimulation may be administered or applied in the form of 25 manually massaging of the mammary gland (the udder, in the case of cows) or by application of a mild, intermittent vacuum, such as the attachment of the milking cups of an automatic milking machine.

It is also to be recognized that alternate modes of administration of the ELA, PGA, somatotropin, and, when optionally included, the dexamethasone may be employed. Such modes of administration include for example, but are not limited to osmotic pump, injection, pellet, pessary, oral, implant, suppository, aerosol, transdermal 5 administration and the use of other delivery devices, which can either be removed at a desired time or used until exhausted of content.

In one preferred embodiment the animal of the method is a dairy heifer that has never been pregnant. In some embodiments it is desirable to use animals that appear to be temporarily or permanently infertile. Those skilled in the art will recognize that the 10 invention may also be employed on animals that are non-pregnant but in declining lactation at the onset of use of the method.

Example 1

Effect of season on induction of lactation was assessed with multiparous cows induced in February (FEB, n=15) or June (JUN, n=18). All cows were reproductive culls 15 which had completed at least one lactation and had obtained an "adjusted milk yield" (305ME) of at least 8,182 kg in their previous lactation. Treatments started on day 0 and consisted of twice daily injections of 17 β -estradiol (0.1mg/kg BW/d) (i.e. 0.1 mg estradiol/kg of body weight/day) and progesterone (0.25 mg/kg BW/d) for 7 d, twice daily mammary massage (2-3 min/gland) for the next 6 days, and an injection of 20 dexamethasone (0.05 mg/kg BW/d) on day 13 of study. Cows also received somatotropin (POSILAC 1 STEP®, 500mg bST) on days 0, 10, 20, and 30 of study and at 14 d intervals thereafter (see Table 1).

Table 1: Treatment Schedule for Induction of lactation

Treatment	Dose	Day of Study	Delivery Route
17 β -estradiol ^a	0.1 mg/kg body weight	0-6	subcutaneous
Progesterone ^a	0.25 mg/kg body weight/day	0-6	subcutaneous
bovine somatotropin (Posilac [®]) ^b	500 mg	0, 10, 20 ,30, and about every 14 days thereafter	subcutaneous
Dexamethasone ^c	0.05 mg/kg body weight	13, administered ~24 hours prior to first milking	intramuscular

^a Sigma, St. Louis Missouri, administered at ~12 hour intervals

^b Monsanto, St. Louis Missouri

^cSchering-Plough, Kenilworth, New Jersey.

5 Milking (3 times/day) commenced on day 14 of study and continued for 122 days. Samples from each milking on a single day in weeks 1, 2, 3, 4, 8, 12 and 16 of lactation were collected for analyses. Cows were considered non-responsive and removed if they failed to produce \geq 9.1 kg of milk on a single day by the 24th day of lactation. Induction was successful if at least one daily total milk yield was \geq 13.6 kg by the 50th day of lactation. Two cows failed to respond in each season and one JUN cow responded but was removed for health reasons on day 12 of lactation. Thus, induction was successful in 10 13 of 15 (86.7%) FEB cows and 15 of 18 (83.3%) JUN cows. Of these cows, one FEB and two JUN cows were removed prior to day 70 of lactation for health reasons. Single milk samples (first milking of the day) were collected from day 1-8 of lactation and analyzed for progesterone and estrogen content (respectively Figure 6 and Figure 7). Additionally, tail vein blood samples were collected from JUN cows on day -6, -3, 0, 1, 15 4, 4, 14, 21, 29, 42, 56, 70, 84, and 112 of lactation. Blood samples were also collected from a group of non-induced, multiparous cows that calved during the two week period when the induced cows received treatments to initiate lactation. All blood samples were analyzed for non-esterified fatty acid (NEFA) content using the NEFA-C[®] kit (Wako 20

Chemicals, Neuss, Germany). The JUN induced cows tended ($P<0.1$) to have greater NEFA concentrations than cows that calved and lactated during the same season.

The shape of the lactation curve was similar for both seasons (see Figure 1). Total 122 day yields of actual milk (2966, 2729 kg), 3.5% Fat-corrected milk (FCM) (3077, 2964 kg), and 4.0% solids-corrected milk (SCM) (2875, 2722 kg) did not differ between seasons. Daily yield per cow averaged 25.0 kg milk, 27.6 kg FCM, and 25.5 kg SCM. Milk composition did not differ between FEB and JUN cows. Milk was discarded from day 0 to day 28 of the study (day 1-14 of lactation). Milk samples were collected from all three milkings on day 7, 14, 21, 28, 56, 84, and 112 of lactation, preserved with 2-bromo-2-nitropropane-1,3diol, and analyzed within two days for fat, total protein, lactose, and somatic cells (see Table 2).

Table 2: Yield and composition of milk from Holstein reproductive culls induced to lactate in late winter (FEB) and early summer (JUN)

Item	FEB	JUN	P-value
Milk Yield-total (kg)			
Actual Milk	2,966	2,729	0.8
3.5% FCM	3,077	2,964	0.9
4.0% SCM	2,875	2,722	0.9
Milk yield-daily (kg/d)			
Actual Milk	25.3	24.7	0.8
3.5% FCM	27.4	27.7	0.9
4.0% SCM	25.6	25.4	0.9
Milk composition			
Fat (%)	4.0	4.5	0.3
Protein ^a (%)	3.5	3.4	0.2
Lactose (%)	4.9	4.9	0.4
Somatic Cells ($10^3/ml$)	159	141	0.8

^a Measured as total protein

In this study, induction was successful in 13 of 15 of FEB cows (86.7%) and 15 of 18 JUN cows (83.3%). The shape of the lactation curve was similar for both seasons (Figure 1) with cows attaining a plateau (about 30 kg of milk/day) by week eight of

lactation. Milk yield and composition did not significantly differ between seasons (Table 2). Furthermore, the results also showed that about 70% of the cows treated using this embodiment surprisingly produced more than 60 lbs. of milk/day and at times averaged production of over 70 lbs. of milk/day (see Figures 2 and 3). Surprisingly, the cows' milk yield was not affected by season. Regardless of the season of induction, adjusted milk yields (305ME) of the induced cows averaged 65% of their 305ME from the previous lactation (Table 3).

Table 3: Adjusted milk yield (305ME) of Holstein reproductive culls during either their induced lactation or after a previous calving

	Previous Yield (kg)	Induced	
		Yield (kg)	% of previous yield
FEB	13,257	8,329	62.8
JUN	12,065	8,004	66.3

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Example 2

Example 2 is a prophetic example using a single administration of 17β -estradiol and single administration of progesterone.

Simple pellets of estradiol benzoate containing approximately 525 mg of estradiol per pellet are produced by compression with an appropriate carrier and administered subcutaneously, the day of administration being defined as day 0. Progesterone pellets containing approximately 1312 mg progesterone per pellet are similarly produced and are administered subcutaneously on day 0. Estradiol is substantially elevated for 10 days in animals administered estradiol pellets. Progesterone is substantially elevated for 7 to 8 days in animals administered progesterone pellets.

A single dose of dexamethasone is given as an intramuscular (IM) injection on day 13. Sustained-release somatotropin (Posilac®) is administered subcutaneously on days 0, 10, 20, 30 and every 14 days after day 30. From day 7 to day 13 udders were massaged twice daily. Milk production is measured for 119 days.

The animals in this example exhibit a surprising response to the method of the present invention, as measured in pounds of milk produced by each animal.

A significant number of the animals produced 30 lb. of milk per day within their first 50 days in milk. The majority of the animals produce greater than 30 lb. of milk per day. By the end of the trial a substantial majority of the cows are averaging 65 lb. of milk per day and surprisingly a majority of the cows were averaging 70 lb. of milk per day. These results are surprising both because of the number of animals that respond to the method and because of the level of response in each animal, as measured in amount of milk produced per day.

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While there is shown and described the a number of exemplary embodiments of the invention, it is to be distinctly understood that this invention is not limited thereto but may be variously embodied to practice the invention.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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